1999-358820/31 B05 **MERE 1997.12.17**
MERCK PATENT GMBH *DE 19756036-A1
1997.12.17 1997-1056036(+1997DE-1056036) *(1999.06.24)* C07D 401/04, A61K 31/405, 31/445, C07D 403/04, 491/10, 401/14, 209/18

New indole amide derivatives - useful as serotonin antagonists and reuptake inhibitors, especially antidepressants and anxiolytics

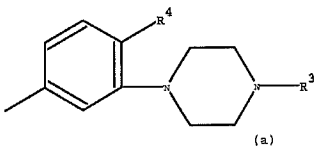
C1999-106360

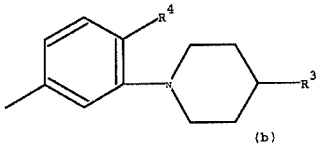
Addnl. Data: MATZEN L, VAN AMSTERDAM C, GREINER H, RAUTENBERG W, BOETTCHER H, BARTOSZYK G, HARTING J

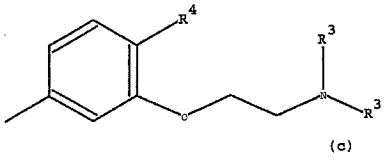
B(6-D1, 14-C3, 14-E10, 14-F2B, 14-J1, 14-L6) .6

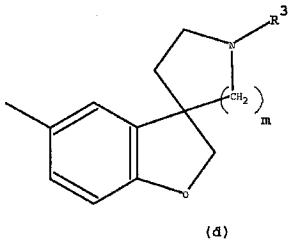
Indole derivatives of formula R^1-$(CH_2)_n$-$(Y)_q$-$(Z)_r$-CO-NH-R^2 (I) and their salts are new.

R^1 = 3-indolyl optionally mono- or disubstituted by A, OA, OH, Hal, CN, NO_2, NH_2, NHA, NA_2, COA, $CONH_2$, CONHA, $CONA_2$, CH_2OH, CH_2OA, CH_2NH_2, CH_2NHA, CH_2NA_2, COOH and/or COOA;
R_2 = a group of formula (a)-(d):
m = 1 or 2;
n = 0-4;
Y = 1,4-cyclohexylene, 1,3-pyrrolidinylene, 1,4-piperazinylene or 1,4-piperidinylene, optionally partially dehydrogenated;









Z = $(CH_2)_n$ or $(CH_2)_nNH$;
q = 0 or 1;
r = 0 or 1;
R^3 = A;
R^4 = OA;
Hal = F, Cl, Br or I;
A = 1-6C alkyl;
provided that r and q are not both 0.

USE

(I) are 5-HT1B/D antagonists and 5-HT (serotonin) reuptake inhibitors especially useful as antidepressants and anxiolytic agents. They can also be used to treat other CNS disorders, inflammation, stroke, side effects of neuroleptics, Parkinson's disease, Alzheimer's disease symptoms, amyotrophic lateral sclerosis, brain and bone-marrow trauma, hypertension, endocrine disorders and gastrointestinal disorders, and as pharmaceutical intermediates.

PREPARATION

Claimed processes include:
(a) reacting R^2NH_2 with R^1-$(CH_2)_n$-$(Y)_q$-$(Z)_r$-CO-L. L = Cl, Br, I or OH; and
(b) reacting R^2NH_2 with R^1-$(CH_2)_n$-$(Y)_q$-$(Z)_r$-H in the presence of a coupling agent such as 1,1'-carbonyldiimidazole, diphosgene, triphosgene or a chloroformate ester.

EXAMPLE

A mixture of 4-methoxy-3-(4-methyl-1-piperazinyl)aniline.2HCl (2.65 g), triethylamine (4.5 ml) and 1,1'-carbonyldiimidazole (1.6 g) in 125 ml MeCN was stirred at room temperature for 3 hr, treated with a suspension of 2 g 5-fluoro-3-(4-piperidinyl)-1H-indole and 1.3 ml triethylamine in 125 ml MeCN,

stirred at room temperature for 12 hr, and worked up. The residue was dissolved in acetone, precipitated with 1N HCl and recrystallised from ethanol/ether to give 4-(5-fluoro-1H-indol-3-yl)-N-(4-methoxy-3-(4-methyl-1-piperazinyl)phenyl)-piperidine-1-carboxamide.HCl, m.pt. 231°C. (CD)
(11pp367DwgNo.0/0)